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NUTRITIVE COMPOSITION BLENDED WITH OLIGOPEPTIDE OF L-GLUTAMINE

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Abstract

PURPOSE:To obtain the title novel composition containing unstable Gln without being restricted by pharmaceutics, showing excellent nutritive effects on various diseases, containing amino acids in a specific composition, by blending an essential amino acid with a nonessential amino acid and an L-Gln residue-containing oligopeptide.
CONSTITUTION:The aimed composition which is obtained by blending an essential amino acid with a nonessential amino acid and an oligopeptide selected from a dipeptide or a tripeptide containing L-glutamine residue, contains amino acids in a composition ratio shown by the table when the oligopeptide is calculated as amino acids, 0.11-7.5 weight ratio of branched-chain amino acids (L- leucine, L-isoleucine and L-valine) based on total amount of L-glutamine, 0.18-0.46 weight ratio of total amounts of the branched-chain amino acids based on total amounts of amino acids and 0.5-1.8 total amounts of nonessential amino acids based on total amounts of essential amino acids.

特許昭63-270557
(S.63.10.25)

英訳はありましたが、
これは海外出願されて
いません。

SPECIFICATION

1. Title of the Invention

NUTRIENT COMPOSITIONS FORMULATED WITH L-GLUTAMINE OLIGOPEPTIDE

2. Claim

A nutrient composition formulated with an essential amino acid, a non-essential amino acid and at least one oligopeptide selected from the group consisting of a dipeptide and a tripeptide containing L-glutamine residue, which at least contains, when said oligopeptide is converted into amino acids, the following amino acids in the following compositional range:

Amino Acid	Compositional Range (g/100 g of total amino acids)
L-isoleucine	4.0 - 13.0
L-leucine	10.0 - 20.0
L-lysine	3.5 - 13.0
L-methionine	1.5 - 10.0
L-phenylalanine	3.0 - 10.0
L-threonine	3.0 - 11.0
L-tryptophan	0.5 - 5.0
L-valine	3.0 - 14.5
L-arginine	3.0 - 12.0
L-histidine	2.0 - 7.0
Glycine	2.0 - 12.0

(cont'd)

Amino Acid	Compositional Range (g/100 g of total amino acids)
L-alanine	3.0 - 15.0
L-cysteine	0 - 1.0
L-aspartic acid	0 - 4.0
L-glutamic acid	0 - 7.0
L-glutamine	5.0 - 40.0
L-proline	1.5 - 5.5
L-serine	0.5 - 3.0
L-tyrosine	0.1 - 5.0

wherein a weight ratio of the total weight of branched chain amino acids (L-leucine, L-isoleucine and L-valine) to the total weight of L-glutamine is 0.11 to 7.50, a weight ratio of the total weight of branched chain amino acids to the total weight of amino acids is 0.18 to 0.46 and a weight ratio of the total weight of the non-essential amino acids to the total weight of the essential amino acids is 0.50 to 1.80.

3. Detailed Description of the Invention

[Field of Industrial Application]

The present invention relates to nutrient compositions and more particularly, to compositions formulated with amino acids used as, e.g., transfusion fluids, which contain an oligopeptide of L-glutamine (Gln) and are suited for nutrient supplementation in various diseases.

[Prior Art]

When patients cannot orally take amino acids or protein in various diseases or in preoperative or postoperative stage, etc. in spite of necessity to take them, or in the case of insufficient intake of amino acids or protein, amino acid transfusion fluids for parenteral application have been widely utilized in these cases for the purpose of nutrient supplementation.

In the case that amino acids are parenterally administered, it is known that it is extremely important to supplement essential or non-essential amino acids in a balanced state, taking an efficiency in the body into account. Most amino acid fluids that have already been clinically used are based on this concept, except for those in use for particular disease. It is also known that a certain group of amino acids play an extremely important role in diseases.

Turning to Gln which is one of non-essential amino acids, transfusion fluids containing Gln have not yet developed. This is because Gln is very unstable and susceptible to decomposition to cause problems in its preparations and a role of Gln is unclear in the living body so that its necessity remains obscure. It is the actual situation that its formulation has been hardly studied.

However, by rapid progress in recent studies relating to amino acid metabolism in disease, importance of Gln has been clarified. The major roles of Gln that have been clarified lie

in improvement in nitrogen balance upon various seizures or stresses, an effect of preventing atrophy of digesting tract mucous membrane which is a severe complication in performing total parenteral nutrition (TPN), an effect of curing wounds, an anti-ulcer effect, etc. Thus, amino acid transfusion fluids in which Gln is formulated are demanded.

With respect to amino acid transfusion fluid containing Gln, some experimental compositions have already been disclosed [(a) DE 320678; (b) Research of Non-Essential Amino Acid, No. 116, 24 (1987); (c) Surgical Forum, 37, 56 (1986)].

However, in (a) described above, it is merely disclosed to use acylated Gln as a new stabilized material for transfusion fluids but its compositions are not studied in detail. Furthermore, examples disclosed in (b) and (c) are to study biological effects after adding a definite amount of unstable crystalline Gln to commercially available amino acid transfusion fluids. No practical composition is presented.

[Problems to be solved by the Invention]

An object of the present invention is to provide amino acid-containing nutrient compositions which contain unstable Gln without any preparatory limitation and can exhibit excellent nutrient effect in a variety of diseases.

[Means for solving the Problems]

Gln is mostly present in plasma or amino acid pool in muscle. Particularly in skeletal muscle, Gln amounts to about 61% of the amino acid pool which is more than the half.

Branched chain amino acids (BCAA) of L-leucine, L-isoleucine and L-valine are also contained in skeletal muscle in large quantities, like Gln.

Furthermore, Gln and BCAA both take an important role in energy generation and improvement in nitrogen balance and are considered to be closely related also to metabolic routes.

Therefore, the present inventors made extensive investigations on amino acid compositions exhibiting excellent effects in a variety of diseases and simultaneously on preparatory stabilization, taking into account that there would be a particular relationship between an amount of Gln to be formulated and an amount of BCAA formulated. As a result, it has been found that instability of Gln can be solved by using Gln as its oligopeptide and in order to exhibit the effects of Gln more effectively, there is a correlation not only to ratios of Gln and BCAA to be formulated but also to ratios of other amino acids to be formulated. Thus, the present invention has come to be accomplished.

That is, the present invention is concerned with a nutrient composition formulated with an essential amino acid, a non-essential amino acid and at least one oligopeptide selected from the group consisting of a dipeptide and a tripeptide containing L-glutamine residue, which at least contains, when said oligopeptide is converted into amino acids, the following amino acids in the following compositional range:

Amino Acid	Compositional Range (g/100 g of total amino acids)
L-isoleucine	4.0 - 13.0
L-leucine	10.0 - 20.0
L-lysine	3.5 - 13.0
L-methionine	1.5 - 10.0
L-phenylalanine	3.0 - 10.0
L-threonine	3.0 - 11.0
L-tryptophan	0.5 - 5.0
L-valine	3.0 - 14.5
L-arginine	3.0 - 12.0
L-histidine	2.0 - 7.0
Glycine	2.0 - 12.0
L-alanine	3.0 - 15.0
L-cysteine	0 - 1.0
L-aspartic acid	0 - 4.0
L-glutamic acid	0 - 7.0
L-glutamine	5.0 - 40.0
L-proline	1.5 - 5.5
L-serine	0.5 - 3.0
L-tyrosine	0.1 - 5.0

wherein a weight ratio of the total weight of BCAA to the total weight of L-glutamine is 0.11 to 7.50, a weight ratio of the total weight of BCAA to the total weight of amino acids is 0.18 to 0.46 and a weight ratio of the total weight of the

non-essential amino acids to the total weight of the essential amino acids is 0.50 to 1.80.

The term "when said oligopeptide is converted into amino acids" refers to "when an amount of the oligopeptide formulated is converted into an amount of each amino acid produced upon complete hydrolysis of the oligopeptide."

Examples of the oligopeptide of Gln used in the present invention include dipeptides such as glycyl-L-glutamine (Gly-Gln), L-alanyl-L-glutamine (Ala-Gln), L-leucyl-L-glutamine (Leu-Gln), L-isoleucyl-L-glutamine (Ile-Gln), L-valyl-L-glutamine (Val-Gln), L-phenylalanyl-L-glutamine (Phe-Gln), L-lysyl-L-glutamine (Lys-Gln), L-arginyl-L-glutamine (Arg-Gln), L-histidyl-L-glutamine (His-Gln), L-threonyl-L-glutamine (Thr-Gln), L-methionyl-L-glutamine (Met-Gln), L-tyrosyl-L-glutamine (Tyr-Gln), etc.; tripeptides such as glycyl-L-glutaminyl-glycine (Gly-Gln-Gly), glycyl-L-glutaminyl-L-alanine (Gly-Gln-Ala), L-alanyl-L-glutaminyl-glycine (Ala-Gln-Gly), L-alanyl-L-glutaminyl-L-alanine (Ala-Gln-Ala), L-leucyl-L-glutaminyl-glycine (Leu-Gln-Gly), L-leucyl-L-glutaminyl-L-alanine (Leu-Gln-Ala), etc. These peptides can be prepared by conventional peptide synthesis.

The amino acid and oligopeptide in accordance with the present invention may be used in their free form or in the form of pharmacologically acceptable salts, for example, metal salts with sodium, potassium, etc.; salts with mineral acids such as hydrochloric acid, sulfuric acid, etc.; salts with organic acids

such as acetic acid, lactic acid, etc. Amino acids other than Gln may also be used as pharmacologically acceptable N-acyl derivatives or ester derivatives or oligopeptides.

The nutrient composition of the present invention is used as a transfusion fluid in many cases but may also be administered to patients who can be orally administered, as solid preparations such as tablets, granules or granulates, etc. Any preparation may be prepared in a conventional manner, using stabilizers, pH regulators, carriers, etc. ordinarily used.

[Functions]

Since Gln is used as its oligopeptide, amino acid compositions containing Gln components stable in preparations can be provided. The composition, namely, nutrient composition of the present invention can prevent atrophy of digesting tract mucous membrane as a complication in performing TPN and can exhibit excellent nutrient effects in various diseases.

The oligopeptide in accordance with the present invention is effectively utilized in the living body.

The present invention is described in more detail by referring to examples and test examples below.

[Example 1]

To the amino acid composition shown in Table 1 was added 24.2 g of Ala-Gln. The mixture was dissolved in distilled water for injection with heating to make the whole volume 0.99 liter. After adjusting its pH to 6.5 with an acetic acid aqueous solution, the whole volume was made 1 liter. The solution was

filtered through a membrane filter having a pore diameter of 0.45 μ. The filtrate was filled in a glass bottle of 200 ml. After replacing with nitrogen gas, the bottle was sealed. The bottle was sterilized with steam under high pressure to prepare a transfusion fluid for parenteral administration.

The preparation contains 9/9 g/l of Ala and 16.3 g/l of Gln when the dipeptide is calculated as each amino acid.

Table 1 Amount of Amino Acids Formulated (g)

Ile	7.6	Trp	1.1	Pro	4.2
Leu	10.8	Val	9.3	Ser	1.4
Lys	5.9	Arg	6.5	Tyr	0.3
Met	3.7	Asp	0.8	Gly	5.5
Phe	5.8	Glu	0.4		
Thr	6.3	His	4.2		

Lys: L-lysine,

Met: L-methionine,

Phe: L-phenylalanine,

Tyr: L-tyrosine,

Trp: L-tryptophan,

Ala: L-alanine,

Arg: L-arginine,

Asp: L-aspartic acid,

Glu: L-glutamic acid,

22.6 g of Gly-Gln. Subsequently, the mixture was treated in a manner similar to Example 1 to give a transfusion fluid for parenteral administration.

When the dipeptide is calculated as each amino acid component, the fluid contains 8.3 g/l of Gly and 16.3 g/l of Gln.

Table 3 Amount of Amino Acids Formulated (g)

Ile	7.5	Trp	1.1	His	4.0
Leu	10.8	Val	9.1	Pro	4.0
Lys	5.9	Ala	8.3	Ser	1.4
Met	3.7	Arg	6.0	Tyr	0.3
Phe	5.8	Asp	0.8		
Thr	6.3	Glu	0.4		

[Examples 4 through 16]

The amino acids and dipeptides shown in Tables 4 through 6 were mixed and the mixture was treated in a manner similar to Example 1 to give transfusion fluids for parenteral administration.

His: L-histidine,

Pro: L-proline,

Ser: L-serine,

Thr: L-threonine,

Gly: glycine

[Example 2]

To the amino acid composition shown in Table 2 were added 19.3 g of Ala-Gln, 15.0 g of Ile-Gln and 5.9 g of Val-Gln. Subsequently, the mixture was treated in a manner similar to Example 1 to give a transfusion fluid for parenteral administration.

When the 3 dipeptides are calculated as each amino acid component, the fluid contains 7.9 g/l of Ala, 7.6 g/l of Ile, 2.8 g/l Val and 25.0 g/l of Gln.

Table 2 Amount of Amino Acids Formulated (g)

Leu	10.8	Trp	1.1	His	4.0
Lys	6.0	Val	4.8	Pro	3.0
Met	3.7	Arg	6.0	Ser	1.4
Phe	5.3	Asp	0.8	Tyr	0.3
Thr	5.1	Glu	0.4	Gly	4.0

[Example 3]

To the amino acid composition shown in Table 3 was added

Table 4 Amounts of Amino Acids and Oligopeptides Formulated (g)

	Example No.				
	4	5	6	7	8
Ile	0	0	15.3	0	0
Leu	13.1	21.0	12.9	18.0	12.9
Lys	4.5	10.0	7.1	7.1	7.1
Met	3.4	2.5	4.4	4.4	4.4
Phe	4.7	5.0	7.0	7.0	7.0
Thr	4.0	15.0	7.5	7.5	6.7
Trp	0.9	2.5	1.3	1.3	1.3
Val	6.3	4.4	11.2	3.3	5.7
Ala	0	5.0	0	7.1	0
Arg	4.3	10.0	8.0	8.0	7.0
Asp	0.6	1.0	1.0	1.0	1.0
Cys	0	1.0	0	0	0
Glu	0.3	2.0	0.5	0.5	0.5
His	2.3	5.0	5.0	5.0	4.0
Pro	2.3	5.0	5.0	5.0	4.0
Ser	1.0	2.5	1.7	1.7	1.5
Tyr	0.3	0.25	0.4	0.4	0.4
Gly	2.9	5.0	5.7	5.7	3.5
Orn	0	2.5	0	0	0
Tau	0	2.5	0	0	0
Ala-Gln	27.3	0	29.7	0	23.2
Ile-Gln	12.1	22.5	0	18.0	18.0
Val-Gln	13.1	17.9	0	16.6	7.1

Table 5 Amounts of Amino Acids and Oligopeptides Formulated (g)

	Example No.				
	9	10	11	12	13
Ile	0	5.6	5.6	5.6	0
Leu	15.7	12.5	13.0	12.5	12.9
Lys	5.2	8.0	8.8	8.8	7.1
Met	3.0	3.1	3.5	3.5	4.4
Phe	5.0	5.0	9.4	9.4	7.0
Thr	5.0	5.0	6.5	6.5	7.5
Trp	1.0	1.3	1.3	1.3	1.3
Val	7.5	4.5	0	4.5	0
Ala	0	0	2.5	5.6	12.2
Arg	5.0	5.0	6.9	6.0	6.0
Asp	0.7	3.8	3.8	1.0	0.8
Cys	0	0	1.0	1.0	0
Glu	0.4	1.35	5.5	5.5	0.4
His	3.5	5.0	8.1	7.1	4.0
Pro	2.3	3.0	3.3	3.3	5.0
Ser	1.2	2.1	2.3	2.3	1.7
Tyr	0.4	0.4	0.4	0.4	0.4
Gly	3.3	2.3	10.7	0	5.0
Ala-Gln	33.5	29.7	9.1	0	0
Gly-Gln	0	0	0	33.4	0
Ile-Gln	14.4	0	11.1	0	18.0
Val-Gln	15.7	0	12.9	0	23.5

Table 6 Amounts of Amino Acids and Oligopeptides Formulated (g)

	Example No.				
	14	15	16	17	18
Ile	5.6	5.6	5.6	9.1	9.1
Leu	12.9	0	0	12.9	12.9
Lys	7.1	8.8	8.8	7.1	0
Met	4.4	3.5	3.5	4.4	4.4
Phe	7.0	9.4	9.4	7.0	7.0
Thr	7.5	6.5	6.5	7.5	7.5
Trp	1.3	1.3	1.3	1.3	1.3
Val	11.2	4.5	4.5	14.0	14.0
Ala	0	0	0	3.1	6.1
Arg	0	6.0	6.0	7.8	6.3
Asp	0.8	3.7	3.7	1.0	0.7
Cys	0	1.0	1.0	0	0
Glu	0.5	5.5	5.2	0.4	0.3
His	5.0	7.1	8.2	4.3	3.5
Pro	5.0	3.3	3.3	4.3	3.5
Ser	1.7	2.3	2.3	1.5	1.2
Tyr	0.4	0.4	0.4	0.3	0.3
Gly	6.0	0	0	6.0	4.8
Ala-Gln	9.1	14.7	0	7.4	0
Gly-Gln	0	0	14.0	0	0
Arg-Gln	13.7	0	0	0	0
Lys-Gln	13.3	0	0	0	16.0

(cont'd)

	Example No.				
	14	15	16	17	18
Leu-Gln-Gly	0	30.1	0	0	0
Leu-Gln-Ala	0	0	31.5	0	0

[Test Example 1]

Using SD strain male rats weighing 170 to 180 g, a silicone rubber catheter was inserted into the right external jugular vein of rat, through which a transfusion fluid was given for a week by total parenteral nutrition.

Given fluids had different amino acid compositions but glucose, electrolytes, vitamins and trace elements were identical. As the amino acids, the amino acid transfusion fluids shown in Examples 1, 2, 3, 4 and 12 and comparative fluids having compositions shown in Table 7 below were used.

The effect was examined in terms of the small intestine. Its indices were weight of jejunum, thickness of jejunal mucous membrane, height of jejunal cilia, DNA in jejunal mucous membrane. The results are shown in Table 8. A clear improvement can be noted as compared to the comparative fluids.

Table 7

Amino Acid and Oligopeptide	Comparative Fluid (g/l) A	B	C
Ile	5.6	9.1	2.8
Leu	12.5	12.9	3.9
Lys	8.8	7.1	5.9
Met	3.5	4.4	2.4
Phe	9.4	7.0	1.7
Thr	6.5	7.5	3.6
Trp	1.3	1.3	1.3
Val	4.5	14.0	3.1
Ala	6.2	7.1	0.9
Arg	7.9	9.0	9.3
Asp	3.8	1.0	0
Cys	1.0	0	1.8
Glu	6.5	0.5	6.6
His	6.0	5.0	2.3
Pro	3.3	5.0	9.3
Ser	2.2	1.7	8.2
Tyr	0.35	0.4	2.0
Gly	10.7	7.0	1.1
Gly-Ala-Gln	0	0	29.9
a Value	0	0	0.62
b Value	0.23	0.36	0.10
c Value	0.92	0.58	3.0

Gly-Ala-Gln : glycyl-L-alanyl-L-glutamine

a Value : total amount of BCAA/Gln (peptide is converted into and calculated as respective amino acids) (w/w)

b Value : total amount of BCAA/total amount of amino acids (peptide is calculated as respective amino acids) (w/w)

c Value : total amount of non-essential amino acids/total amount of essential amino acids (w/w)

Table 8 Measurement Data on Jejunum

	Weight of Jejunum (mg/cm)	Thickness of Jejunal Mucous Membrane (mm)	Height of Jejunal Cilia (mm)	DNA in Jejunal Mucous Membrane (μg/g)
Example 1	32.0 ± 0.3	0.57 ± 0.09	0.32 ± 0.08	127.0 ± 6.5
Example 2	34.0 ± 0.3	0.59 ± 0.08	0.38 ± 0.08	131.0 ± 9.9
Example 3	33.4 ± 0.4	0.57 ± 0.10	0.34 ± 0.10	129.0 ± 8.4
Example 4	34.5 ± 0.3	0.60 ± 0.09	0.36 ± 0.08	152.0 ± 10.8
Example 12	35.7 ± 0.7	0.61 ± 0.10	0.39 ± 0.06	155.0 ± 10.2
Comparative Fluid A	25.0 ± 0.6	0.55 ± 0.11	0.29 ± 0.09	105.0 ± 8.1
Comparative Fluid B	27.0 ± 0.5	0.53 ± 0.13	0.30 ± 0.05	118.0 ± 7.8
Comparative Fluid C	25.2 ± 0.4	0.51 ± 0.12	0.28 ± 0.06	119.5 ± 7.4
Control	50.1 ± 0.3	0.77 ± 0.10	0.67 ± 0.08	198.3 ± 9.8

[Test Example 2]

5-Fluorouracil (5-FU) was orally given to SD strain male rats (5 per one group) weighing 160 to 170 g, which had been fasted overnight, in a dose of 200 mg to prepare model rats with small intestine disorder. Next, a silicone rubber catheter was inserted into the right external jugular vein, through which a transfusion fluid was given for 5 days by total parenteral nutrition. As transfusion fluids, the amino acid transfusion fluids obtained in Examples 2 and 3 and comparative fluid A shown in Table 7 were used. With respect to groups administered with the respective fluids, nutrition effect (change in body weight, accumulated nitrogen balance) and enzyme activity (alkaline phosphatase activity, sucrase activity) in jejunal mucous membrane were examined.

The results are shown in Figs. 1 and 2 and Table 9. It is noted that the amino acid transfusion fluids of Examples 2 and 3 showed significantly excellent nutrition effect and high enzyme activity in jejunal mucous membrane, as compared to comparative fluid A.

Table 9 Enzyme Activity in Jejunal Mucous Membrane

Fluid	Alkaline Phosphatase Activity (IU/cm)	Sucrase Activity (IU/cm)
Example 2	679 ± 349	15.3 ± 2.5
Example 3	657 ± 310	14.6 ± 3.9
Comparative Fluid A	426 ± 242	9.4 ± 2.4
Control	1050 ± 431	24.2 ± 2.9

[Effects of the Invention]

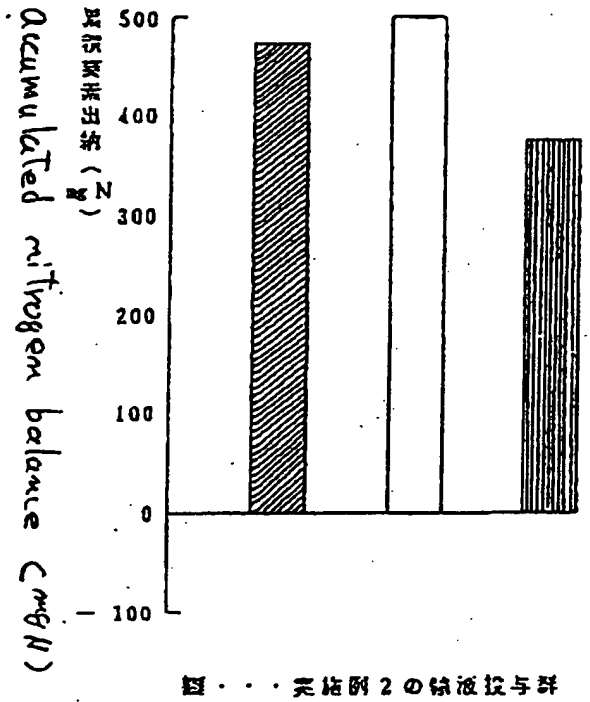
According to the present invention, new nutrient fluid compositions formulated with amino acids which contain unstable Gln without any preparatory restriction and can exhibit excellent nutrient effects in various diseases can be provided.

4. Brief Description of the Drawings

Fig. 1 shows change in body weight increment of rats with small intestine disorders when transfusion fluids were administered. Fig. 2 indicates accumulated nitrogen balance.

Fig 2

図 2



▨・・・実施例2の輸液投与群 " Experimental 2

□・・・実施例3の輸液投与群 " " 3

▥・・・比較液Aの輸液投与群 " with Comparative fluid

表 9

試験液	アルカリフォスファターゼ活性 (IU/ml)	シュクラーゼ活性 (IU/ml)
実施例 2	679 ± 349	15.3 ± 2.5
実施例 3	657 ± 310	14.6 ± 3.9
比較液 A	426 ± 242	8.4 ± 2.4
無投与	1050 ± 431	24.2 ± 2.9

（発明の効果）

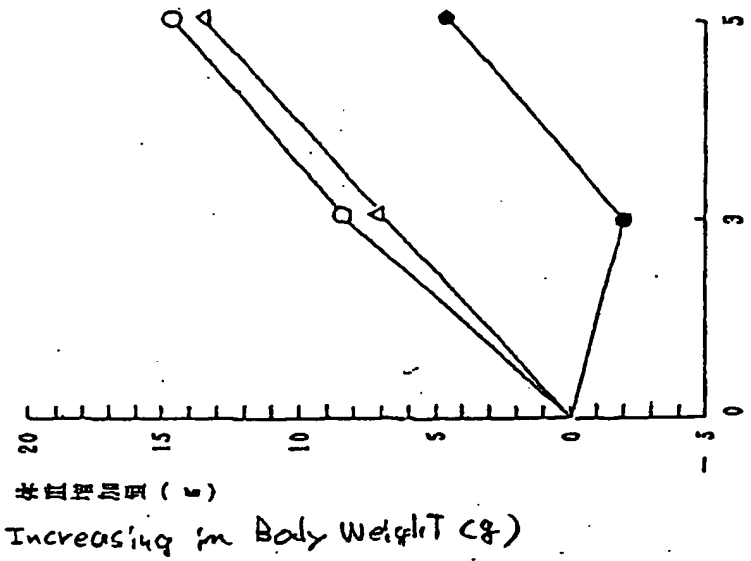
本発明によれば、不安定なCl₂を実質的に含有せず、且つ各種疾患時に優れた栄養効果を発揮する新しい処方のアミノ酸配合栄養組成物を提供することができる。

4．図面の簡単な説明

図1は、試液投与した小腸near-ラットの体重増加量の推移を示し、図2は実施例1の結果出納を示す。

特許出願人　日本製薬株式会社

Fig 1
図 1



○・・・実施例2の試液投与群 groups administrated with the fluid in Experimental 2.
△・・・実施例3の試液投与群 〃 Experimental 3
●・・・比較液Aの試液投与群 〃 with comparative fluid A.